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(19)

(54) 2-SUBSTITUTED-1-(OMEGA-AMINOALKOXY) BENZENES

(71) We, MITSUBISHI CHEMICAL INDUSTRIES LIMITED, a Japanese Body Corporate, of 5—2, Marunouchi 2-chome, Chiyoda-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 2-substituted-1-(omega-aminoalkoxy) benzenes and provides compounds which are pharmacologically active as antidepressants.

L. C. Cheney et al, J. Am. Chem. Soc., Vol. *71*, 60—64 (1949) describes several diphenylmethanes containing a substituent at the 2-position, including 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-morpholinoethoxy, 2-(1-piperidyl)ethoxy, 2-isopropylaminoethoxy, 3-(1-piperidyl) propoxy, 3-dimethylaminopropoxy and 3-dibutylaminopropoxy.

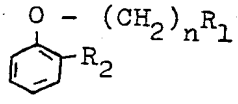
That reference also indicates that 2-(2-aminoethoxy)diphenylmethanes and 2-(3-aminopropoxy)diphenylmethanes have antihistaminic and local anaesthetic activity in animals.

However, it is to be noted that the 2-(4-aminobutoxy)diphenylmethanes and 2-(5-aminopentyloxy)diphenylmethanes of this invention are not described in that reference.

It is also to be noted that there is no indication in that reference that the 2-omega-aminoalkoxydiphenylmethanes possess antidepressant activity.

As a matter of fact, the 2-(3-dimethylaminopropoxy)diphenylmethane which is described in that reference does not possess antidepressant activity according to pharmacological testing.

This invention provides a compound having the general formula:



(I)

wherein R_1 is amino, C_1 to C_3 alkylamino, C_2 to C_6 dialkylamino morpholino, or 1-piperidyl, R_2 is benzyl, phenoxy, phenylthio, 1-phenylethyl or phenyl and n is 3, 4 or 5, provided that when R_2 is benzyl and n is 4 or 5 R_1 is C_1—C_3 alkylamino or 1-

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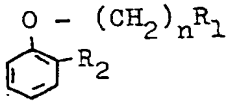
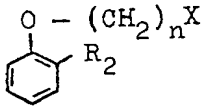
piperidyl; when R_2 is benzyl and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenoxy R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4 or 5; when R_2 is phenylthio and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenylthio and n is 4 R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino or morpholino; when R_2 is phenylthio and n is 5 R_1 is C_2—C_6 dialkylamino or morpholino; when R_2 is 1-phenylethyl and n is 4 R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino; when R_2 is 1-phenylethyl and n is 3 R_1 is dimethylamino; and when R_2 is phenyl R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4; or a pharmaceutically acceptable acid addition salt of a compound of Formula I.

This invention also provides a process for producing a compound having the formula:



(I)

wherein R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino, morpholino, or 1-piperidyl; R_2 is benzyl, phenoxy, phenylthio, 1-phenylethyl or phenyl; and n is 3, 4 or 5, which process comprises reacting a 2-substituted-1-(omegahalogenalkoxy) benzene of the formula:



(II)

wherein X is halogen; and R_2 and n are as defined above, with an amine of the formula:

$$R_1—H \qquad \text{(III)}$$

wherein R_1 is as defined above, provided that when R_2 is benzyl and n is 4 or 5 R_1 is C_1—C_5 alkylamino or 1-piperidyl; when R_2 is benzyl and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenoxy R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4 or 5; when R_2 is phenylthio and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenylthio and n is 4 R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino or morpholino; when R_2 is phenylthio and n is 5 R_1 is C_2—C_6 dialkylamino or morpholino; when R_2 is 1-phenylethyl and n is 4 R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino; when R_2 is 1-phenylethyl and n is 3 R_1 is dimethylamino; and when R_2 is phenyl R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4.

The present invention includes a method for palliating conditions of depression in warm-blooded animals which method comprises administering to said animal an amount effective as an antidepressant of a compound of Formula I of the invention.

As summarized above, this invention relates to a group of compounds useful as pharmaceutical agents, which compounds are represented by Formula I above.

Illustrative of the compounds of this invention are the following:

2-(4-methylaminobutoxy)diphenylmethane
2-(4-ethylaminobutoxy)diphenylmethane
2-(5-methylaminopentyloxy)diphenylmethane
2-[4-(1-piperidyl)butoxy]diphenylmethane
2-(4-aminobutoxy)diphenyl ether
2-(4-methylaminobutoxy)diphenyl ether
2-(4-dimethylaminobutoxy)diphenyl ether
2-(5-methylaminopentyloxy)diphenyl ether
2-(5-dimethylaminopentyloxy)diphenyl ether
2-(3-methylaminopropoxy)diphenyl sulfide
2-(4-aminobutoxy)diphenyl sulfide
2-(4-methylaminobutoxy)diphenyl sulfide
2-(4-dimethylaminobutoxy)diphenyl sulfide

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2-(4-morpholinobutoxy)diphenyl sulfide
2-(5-dimethylaminopentyloxy)diphenyl sulfide
2-(3-methylaminopropoxy)diphenylmethane
2-(3-ethylaminopropoxy)diphenylmethane
2-(3-dimethylaminopropoxy)diphenylmethylmethane
2-(4-aminobutoxy)diphenylmethylmethane
2-(4-methylaminobutoxy)diphenylmethylmethane
2-(4-dimethylaminobutoxy)diphenylmethylmethane
2-(4-aminobutoxy)diphenyl
2-(4-methylaminobutoxy)diphenyl
2-(4-ethylaminobutoxy)diphenyl
2-(4-isopropylaminobutoxy)diphenyl
2-(4-dimethylaminobutoxy)diphenyl

The pharmaceutically acceptable acid addition salts of the above compounds are, of course, also included within the scope of this invention.

It will be understood that the term "pharmaceutically acceptable acid addition salts" as used herein includes non-toxic salts of the compounds of this invention with an anion. Representative of such salts are hydrochlorides, hydrobromides, sulfates, phosphates, nitrates, acetates, succinates, adipates, propionates, tartrates, maleates, citrates, benzoates, toluenesulfonates, and methanesulfonates.

Of the compounds of this invention, it will be understood that the following compounds are most preferred due to their high level of antidepressant activity and their low level of toxicity:—

2-(4-methylaminobutoxy)diphenylmethane
2-(4-ethylaminobutoxy)diphenylmethane
2-(5-methylaminopentyloxy)diphenylmethane
2-(4-methylaminobutoxy)diphenyl ether
2-(4-dimethylaminobutoxy)diphenyl ether
2-(5-methylaminopentyloxy)diphenyl ether
2-(3-methylaminopropoxy)diphenyl sulfide
2-(4-methylaminobutoxy)diphenyl sulfide
2-(4-dimethylaminobutoxy)diphenyl sulfide
2-(3-methylaminopropoxy)diphenylmethane
2-(4-methylaminobutoxy)diphenylmethylmethane
2-(4-dimethylaminobutoxy)diphenylmethylmethane
2-(3-dimethylaminopropoxy)diphenylmethylmethane
2-(4-methylaminobutoxy)diphenyl
2-(4-aminobutoxy)diphenyl
2-(4-dimethylaminobutoxy)diphenyl

The compounds of this invention are prepared in accordance with the process of the invention by reacting a 2-substituted-1-(omega-halogenoalkoxy)benzene with an amine. The 2-substituted-1-(omega-halogenoalkoxy)benzene starting materials which are represented by Formula II above can be prepared by reacting a 2-substituted phenol with a 1,3-dihalogenopropane, 1,4-dihalogenobutane or 1,5-dihalogenopentane in the presence of an alkali.

The amine starting materials which are represented by Formula III above include ammonia; primary amines such as methylamine, ethylamine, isopropylamine and the like; secondary amines such as dimethylamine, diethylamine, N-methylethylamine and the like; morpholine; piperidine.

The amine reacts with an equimolecular amount of the 2-substituted-1-(omega-halogenoalkoxy)benzene. However, the use of the excess amine accelerates the reaction. Normally, the amount of the amine to be employed is in the range of 1 to 100 moles per mole of the 2-substituted-1-(omega-halogenoalkoxy)benzene.

The reaction can be carried out without an added solvent. However, the use of a reaction-inert solvent makes a homogeneous reaction possible.

Examples of such solvents are water, dioxane, tetrahydrofuran, dimethyl sulfoxide, lower aliphatic alcohols and the mixture thereof.

The reaction temperature is not critical, but normally ranges from room temperatures to 150°C.

The reaction time varies widely with the reaction temperature and the

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reactivity of the starting materials, but normally is in the range of from 10 to 40 hours.

The presence of bases which neutralize a hydrogen halide formed in the course of the reaction accelerates the reaction.

Examples of such bases are inorganic bases such as potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate and the like; and tertiary amines such as pyridine, triethylamine and the like.

The amount of the base to be employed is normally in the range of 1 to 5 moles per mole of the 2-substituted-1-(omega-halogenoalkoxy)benzene.

When the base is absent, the 2-substituted-1-(omega-aminoalkoxy)benzenes react with a hydrogen halide formed during the reaction, and are converted to the acid addition salts thereof.

Acid addition salts of the 2-substituted-1-(omega-aminoalkoxy)benzenes may be conveniently prepared by contacting the compounds with a suitable acid.

The 2-substituted-1-(omega-aminoalkoxy)benzenes and the acid addition salts thereof may be purified by recrystallization employing a suitable solvent such as alcohol-ether.

Pharmacological testing of the 2-substituted-1-(omega-aminoalkoxy)benzenes has demonstrated that they are useful as antidepressant agents as evidenced by their ability to reverse reserpine hypothermia in mice.

Anticonvulsant activity has also been found in the compounds of this invention.

The compounds have been tested in mice for antidepressant, sedative, anticonvulsant and anticholinergic activity.

The compounds were administered intraperitoneally and the activities of the compounds were compared with those of Amitriptyline.

Antidepressant activity was evaluated by antagonism of reserpine (5 mg/kg i.p.) induced hypothermia (P. S. J. Spencer in "Antidepressant Drugs" S. Garattini and M. N. G. Duhes, ed., Excerpta Medica Foundation, Amsterdam, pages 194—204 (1967)) and antireserpine activity was expressed as relative potency (Amitriptyline=1).

LD50 was calculated by Litchfield-Wilcoxon method.

CNS depressant activity was defined by the ability of the compounds to cause neurological deficit as measured by traction test (S. Courvoisier, R. Ducrot, L. Julou; "Psychotropic Drugs" ed. by S. Garattini, V. Ghetti, page 373/4, (1957)) and spontaneous motor activity (Spontaneous motor activity was measured by ANIMEX apparatus).

Anticonvulsant activity was determined by antagonism of electroshock induced tonic extensor (L. S. Goodman, M. Singh Grewal, W. C. Brown and E. A. Swinyard, J. Pharmacol, Exptal. Therap., *108*, 168 (1953)).

Central anticholinergic effect was assessed by testing the tremorine induced tremor in mice (G. M. Everett, L. E. Bloucus and J. M. Sheppard, Science *124* 79 (1956)).

Results are summarized in Table I and Table II, in which ED50 is defined as the dose of the test compounds, which prevent 50% of each response.

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TABLE I

Antireserpine Activity in Mice

Compound	Relative Potency	LD50 (mg/kg i.p.)
2-(4-methylaminobutoxy)diphenyl-methane hydrochloride	0.73	173
2-(4-ethylaminobutoxy)diphenyl-methane hydrochloride	0.53	120
2-(5-methylaminopentyloxy)diphenylmethane hydrochloride	0.54	160
*2-(3-dimethylaminopropoxy)-diphenylmethane hydrochloride	0.00	
2-(4-methylaminobutoxy)diphenyl ether hydrochloride	1.10	100
2-(4-dimethylaminobutoxy)-diphenyl ether hydrochloride	0.58	92
2-(5-methylaminopentyloxy)-diphenyl ether hydrochloride	0.57	85
2-(4-methylaminobutoxy)diphenyl sulfide hydrochloride	0.90	120
2-(4-dimethylaminobutoxy)-diphenyl sulfide hydrochloride	0.70	130
2-(3-methylaminopropoxy)-diphenyl sulfide hydrochloride	0.60	135
2-(3-methylaminopropoxy)-diphenylmethane hydrochloride	0.56	160
*2-(3-dimethylaminopropoxy)diphenylmethane hydrochloride	0.00	–
*2-(2-dimethylaminoethoxy)diphenylmethane hydrochloride	0.00	–
*2-(2-methylaminoethoxy)diphenylmethane hydrochloride	0.00	–
2-(4-methylaminobutoxy)diphenylmethylmethane hydrochloride	0.66	140
2-(4-dimethylaminobutoxy)diphenylmethylmethane hydrochloride	0.36	110
2-(3-dimethylaminopropoxy)diphenylmethylmethane hydrochloride	0.34	155
2-(4-methylaminobutoxy)diphenyl hydrochloride	0.99	78
2-(4-aminobutoxy)diphenyl hydrochloride	0.59	137
2-(4-dimethylaminbutoxy)diphenyl hydrochloride	0.45	100
Amitriptyline	1.00	65

* Comparative

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TABLE II

CNS Depressant, Anticonvulsant and Central Anticholinergic Activity in Mice

Compound	Anti-Convulsant Activity ED50 (mg/kg i.p.)	Muscle Relaxant Action ED50 (mg/kg i.p.)	Spontaneous Motor Activity Depression ED50 (mg/kg i.p.)	Antitremorine Effect ED50 (mg/kg i.p.)
2-(4-methylaminobutoxy)-diphenylmethane hydrochloride	45	80	70	>60
2-(4-methylaminobutoxy)-diphenyl ether hydrochloride	32	60	60	30
2-(4-methylaminobutoxy)-diphenyl sulfide hydrochloride	>60	50	>60	30
2-(3-methylaminopropoxy)-diphenylmethane hydrochloride	40	65	90	42
2-(4-methylaminobutoxy)-diphenylmethylmethane hydrochloride	25	>60	32	20
2-(4-methylaminobutoxy)-diphenyl hydrochloride	14	40	30	20
2-(4-aminobutoxy)-diphenyl hydrochloride	14	50	40	60
Amitriptyline	16	15	18	4

It will be apparent from Tables I and II that the 2-substituted-1-(omega-aminoalkoxy)benzenes exhibit antireserpine activity comparable to that of Amitriptyline, while they exhibit low toxicity, weak CNS depressant and anticholinergic action.

The compounds of this invention can be administered by any means that effects palliating conditions of depression in warm-blooded animals.

For example, administration can be parenterally, e.g. subcutaneously, intravenously, intramuscularly, or intraperitoneally. Alternatively or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health and weight of the recipient, the extent of depression, kind of concurrent treatment if any, frequency of treatment, and the nature of the effect desired. Generally, a daily dosage of the active ingredient compound will be from about 0.5 to 50 mg per kg of body weight. Normally, from 1 to 30 mg per kg per day, in one or more applications per day is effective to obtain the desired result.

The compound of Formula I can be employed in dosage forms such as tablets, capsules, powder packets, or liquid solutions, suspensions, or elixirs, for oral adminisitration, or sterile liquid formulations such as solutions or suspensions for parenteral use. In such compositions, the active ingredient will ordinarily always be present in an amount of at least 0.5% by weight on the total weight of the composition and not more than 90% by weight.

Besides the active ingredient of this invention, the composition will contain a solid or liquid non-toxic pharmaceutical carrier for the active ingredient. In one embodiment of a composition, the solid carrier can be a capsule of the ordinary gelatin type. In the capsule will be from about 30—60% by weight of a compound of Formula I and 70—40% of a carrier. In another embodiment, the active ingredient can be tableted with or without adjuvants, or put into powder packets. These capsules, tablets and powders will generally contain from about 5% to about 95% and preferably from 25% to 90% by weight of the active ingredient. These dosage forms preferably contain from about 5 to about 500 mg of active ingredients, with from about 25 to about 250 mg being most preferred.

The pharmaceutical carrier can be a sterile liquid such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like.

In general, water saline, aqueous dextrose and related sugar solutions, and glycols such as propylene glycol and polyethylene glycol are preferred liquid carriers, particularly for injectable solutions such as saline will ordinarily contain from about 0.5% to 20% and preferably about 1 to 10% by weight of the active ingredient.

As mentioned above, oral administration can be in a suitable suspension or syrup, in which the active ingredient normally will constitute from about 0.5 to 10% by weight.

The pharmaceutical carrier in such composition can be a watery vehicle such as an aromatic water, a syrup or a pharmaceutical mucilage.

The following examples are presented to further illustrate the preparation of the compounds of this invention.

Example 1.

A solution of 5.0 g of 2-(4-bromobutoxy)diphenyl ether 30 ml of 40% dimethylamine aqueous solutions, and 100 ml of ethanol is allowed to stand at room temperature for 8 hours. Ethanol and excess dimethylamine are distilled in vacuo, 2N-NaOH aqueous solution is added, and the reaction product is extracted with ether. The ether solution is distilled, 2N-HCl solution is added and the solution is evaporated to dryness.

The residue is recrystallized from ethanol-ether to give 4.6 g (89% yield) of 2-(4-dimethylaminobutoxy)diphenyl ether hydrochloride, m.p. 131—135°C.
Analysis—Calcd. for $C_{18}H_{23}NO_2.HCl$ (percent): C, 67.17; H, 7.52; N, 4.35.
Found (percent): C, 67.35; H, 7.46; N, 4.25.

Example 2.

A solution of 5.0 g of 2-(5-bromopentyloxy)diphenyl ether and 6 g of methylamine in 100 ml of ethanol is heated at a temperature of 50°C for 2 hours in a sealed tube.

Ethanol and excess methylamine are distilled in vacuo, 2N-NaOH aqueous solution is added, and the reaction product is extracted with ether. Dry hydrogen chloride gas is passed into the ether solution, and the precipitate collected by filtration. Recrystallization from ethanol-ether gives 4.2 g (88% yield) of 2-(5-methylaminopentyloxy)diphenyl ether hydrochloride, m.p. 88—90°C.
Analysis—Calcd. for $C_{18}H_{23}NO_2.HCl$ (percent): C, 67.17; H, 7.52; N, 4.35.
Found (percent): C, 67.30; H, 7.64; N, 4.37.

Example 3.

A solution of 5.0 g of 2-(4-bromobutoxy)diphenyl in 10 g of isopropylamine is allowed to stand at room temperature for 5 hours.

Isopropylamine is evaporated in vacuo, 2N-NaOH aqueous solution is added, and the reaction product is extracted with ether. The ether solution is distilled, 2N-HCl solution is added, and the solution is evaporated to dryness. The residue is recrystallized from ethanol-ether to give 4.5 g (88% yield) of 2-(4-isopropylaminobutoxy)diphenyl hydrochloride, m.p. 172—177°C.
Analysis—Calcd. for $C_{19}H_{25}ON.HCl$ (percent): C, 71.34; H, 8.19; N, 4.38.
Found (percent): C, 70.95; H, 7.94; N, 4.48.

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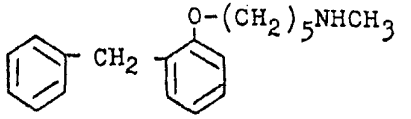
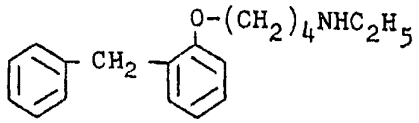
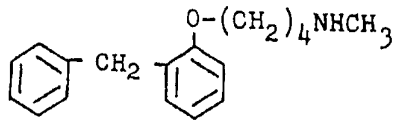
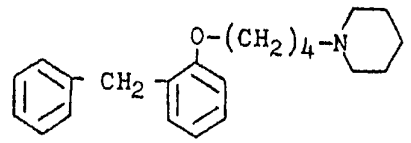
Example 4—26.
The compounds in the following table were prepared according to the procedure described in Example 1, 2 or 3 using the appropriate starting materials.

Example No.	Compound		Preparation Process (Ex. No.)	m. p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
4		HCl	2	87.5-89.5	71.34 71.34	8.19 8.30	4.38 4.27
5		HCl	2	104-106	71.34 71.29	8.19 8.32	4.38 4.15
6		HCl	1	114-119	70.68 70.93	7.91 7.99	4.58 4.35
7		HCl	1	139-142	73.41 73.09	8.40 8.21	3.89 3.61

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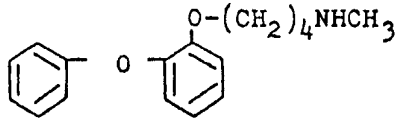
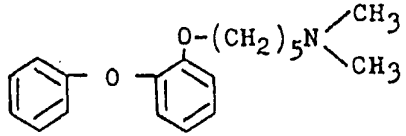
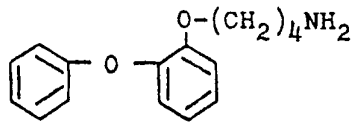
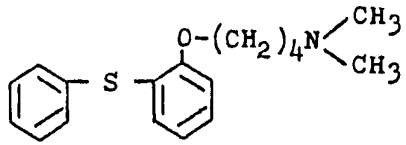
Example No.	Compound		Preparation Process (Ex. No.)	m. p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
8.		HCl	2	112-116	66.33 66.60	7.20 7.18	4.55 4.47
9		HCl	1	104-108	67.94 67.85	7.80 7.93	4.17 4.16
10		HCl	1	93-95	65.41 65.70	6.86 6.96	4.77 4.66
11		HCl	1	140-146	63.98 63.84	7.16 7.19	4.15 3.96

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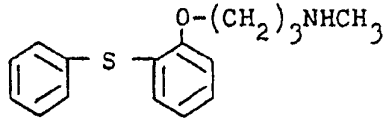
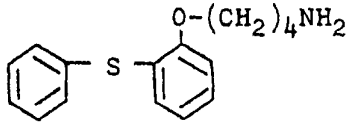
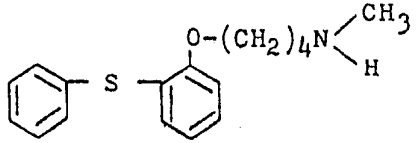
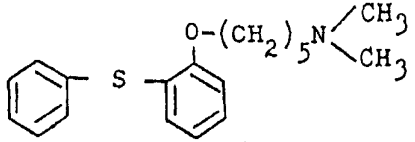
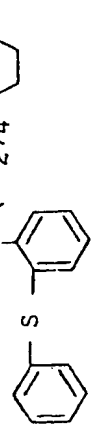
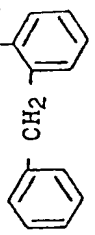
Example No.	Compound		Preparation Process (Ex. No.)	m. p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
12		HCl	2	99-102	62.02 61.84	6.51 6.35	4.52 4.42
13		HCl	1	78-81	62.02 61.98	6.51 6.50	4.52 4.39
14		HCl	1	143-147	63.04 63.15	6.85 6.87	4.33 4.26
15		HCl	2	95-96	64.84 64.81	7.45 7.45	3.98 3.89

Example No.	Compound		Preparation Process (Ex. No.)	m.p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
16		HCl	1	106-109	63.22 63.20	6.90 6.89	3.69 3.61
17		HCl	1	148-152	69.97 70.03	7.60 7.40	4.80 4.58

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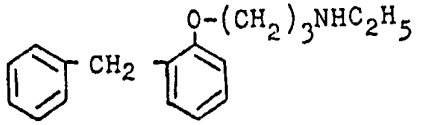
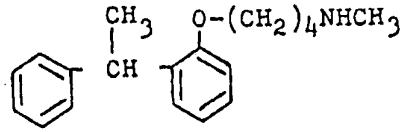
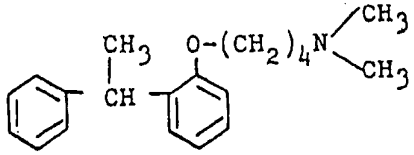
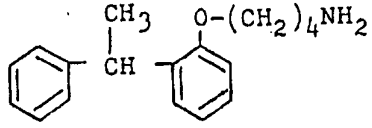
Example No.	Compound		Preparation Process (Ex. No.)	m. p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
18		HCl	1	153-154	70.68 70.69	7.91 7.91	4.58 4.48
19		HCl	1	155-158	71.34 71.05	8.19 8.31	4.38 4.41
20		HCl	2	117.5-119	71.94 71.80	8.45 8.58	4.20 4.05
21		HCl	1	109-111	70.68 70.83	7.91 7.88	4.58 4.54

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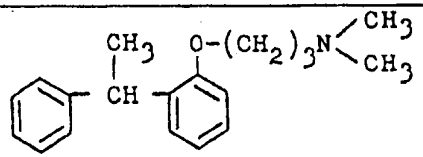
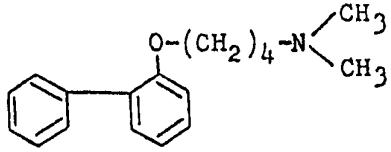
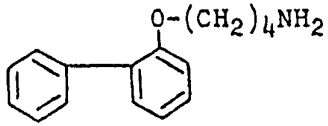
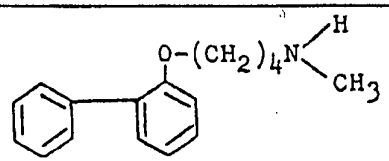
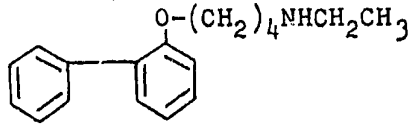
Example No.	Compound		Preparation Process (Ex. No.)	m. p. (°C)	Analysis Upper: Calcd. Lower: Found		
	Formula	Addition Moiety			C	H	N
22		HCl	2	142-144	71.34 71.25	8.19 8.08	4.38 4.25
23		HCl	1	115-118	70.68 70.95	7.91 7.94	4.58 4.48
24		HCl	1	155-158	69.18 69.06	7.26 7.32	5.04 5.15
25		HCl	1	142-144	69.97 70.10	7.60 7.85	4.80 4.61
26		HCl	1	146-148	70.68 71.00	7.91 8.04	4.58 4.54

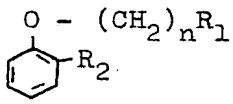
Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the scope of the invention as set forth herein.

No claim is made herein to any method when used for the treatment or prevention of disease in human beings.

Subject to the foregoing disclaimer

WHAT WE CLAIM IS:—

1. A compound having the general formula



(I)

wherein R_1 is amino, C_1 to C_5 alkylamino, C_2 to C_6 dialkylamino or morpholino, or 1-piperidyl, R_2 is benzyl, phenoxy, phenylthio, 1-phenylethyl or phenyl and n is 3, 4 or 5, provided that when R_2 is benzyl and n is 4 or 5 R_1 is C_1—C_5 alkylamino or 1-piperidyl; when R_2 is benzyl and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenoxy R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4 or 5; when R_2 is phenylthio and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenylthio and n is 4 R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino or morpholino; when R_2 is phenylthio and n is 5 R_1 is C_2—C_6 dialkylamino or morpholino; when R_2 is 1-phenylethyl and n is 4 R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino; when R_2 is 1-phenylethyl and n is 3 R_1 is dimethylamino; and when R_2 is phenyl R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4; or a pharmaceutically acceptable acid addition salt of a compound of Formula I.

2. A compound as claimed in claim 1 wherein R_1 is methylamino, ethylamino, isopropylamino, or dimethylamino.

3. A compound as claimed in claim 1 wherein R_2 is benzyl; and n is 4 or 5.

4. A compound as claimed in claim 1 wherein R_2 is phenoxy.

5. A compound as claimed in claim 1 wherein R_2 is phenylthio; and n is 3, 4 or 5.

6. A compound as claimed in claim 1 wherein R_2 is benzyl; and n is 3.

7. A compound as claimed in claim 1 wherein R_2 is 1-phenylethyl.

8. A compound as claimed in claim 1 wherein R_2 is phenyl.

9. A compound as claimed in claim 3, which is 2-(4-methylaminobutoxy)-diphenylmethane.

10. A compound as claimed in claim 3, which is 2-(4-ethylaminobutoxy)-diphenylmethane.

11. A compound as claimed in claim 3, which is 2-(5-methylamino-pentyloxy)-diphenylmethane.

12. A compound as claimed in claim 4, which is 2-(4-methylaminobutoxy)-diphenyl ether.

13. A compound as claimed in claim 4, which is 2-(4-dimethylaminobutoxy)-diphenyl ether.

14. A compound as claimed in claim 4, which is 2-(5-methylaminopentyloxy)-diphenyl ether.

15. A compound as claimed in claim 5, which is 2-(3-methylaminopropoxy)-diphenyl sulfide.

16. A compound as claimed in claim 5, which is 2-(4-methylaminobutoxy)diphenyl sulfide.

17. A compound as claimed in claim 5, which is 2-(4-dimethylaminobutoxy)-diphenyl sulfide.

18. A compound as claimed in claim 6, which is 2-(3-methylaminopropoxy)-diphenylmethane.

19. A compound as claimed in claim 7, which is 2-(4-methylaminobutoxy)-diphenylmethylmethane.

20. A compound as claimed in claim 7, which is 2-(4-dimethylaminobutoxy)-diphenylmethylmethane.

21. A compound as claimed in claim 7, which is 2-(3-dimethylaminopropoxy)-diphenylmethylmethane.

22. A compound as claimed in claim 8, which is 2-(4-methylaminobutoxy)-diphenyl.

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23. A compound as claimed in claim 8 which is 2-(4-aminobutoxy)diphenyl.

24. A compound as claimed in claim 8, which is 2-(4-dimethylaminobutoxy)diphenyl.

25. A compound as claimed in claim 1 and identified as the product in any one of Examples 1 to 3, 7 to 11, 13, 15 to 18, 20, 21 or 26.

26. A pharmaceutical composition comprising a compound as claimed in any preceding claim and a pharmaceutical carrier therefor.

27. A pharmaceutical product in unit dosage form comprising a compound as claimed in any one of claims 1 to 25 in the form of a capsule, tablet or packeted powder.

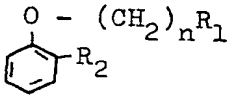
28. A pharmaceutical product as claimed in claim 27 comprising a composition as claimed in claim 26, wherein the carrier is a solid carrier and the composition contains from 25 to 90% of the compound of Formula I.

29. A pharmaceutical composition as claimed in claim 26, wherein the carrier is sterile water, peanut oil, sesame oil, soybean oil, mineral oil, saline, aqueous dextrose solution, propylene glycol or polyethylene glycol.

30. A pharmaceutical composition as claimed in claim 29 wherein the pharmaceutical composition contains from 1 to 10% by weight of the compound of Formula I.

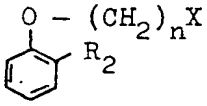
31. A pharmaceutical composition as claimed in claim 26 for oral administration comprising, as carrier, an aromatic water, a syrup, or pharmaceutical mucilage and containing from 0.5 to 10% by weight of the compound of Formula I.

32. A process for producing a compound having the formula:



(I)

wherein R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino, morpholino, or 1-piperidyl; R_2 is benzyl, phenoxy, phenylthio, 1-phenylethyl or phenyl- and n is 3, 4 or 5, which process comprises reacting a 2-substituted-1-(omegahalogenoalkoxy)benzene of the formula:



(II)

wherein X is halogen; and R_2 and n are as defined above, with an amine of the formula:

$$R_1—H \qquad \text{(III)}$$

wherein R_1 is as defined above, provided that when R_2 is benzyl and n is 4 or 5 R_1 is C_1—C_5 alkylamino or 1-piperidyl; when R_2 is benzyl and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenoxy R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4 or 5; when R_2 is phenylthio and n is 3 R_1 is C_1—C_5 alkylamino; when R_2 is phenylthio and n is 4 R_1 is amino, C_1—C_5 alkylamino, C_2—C_6 dialkylamino or morpholino; when R_2 is phenylthio and n is 5 R_1 is C_2—C_6 dialkylamino or morpholino; when R_2 is 1-phenylethyl and n is 4 R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino; when R_2 is 1-phenylethyl and n is 3 R_1 is dimethylamino; and when R_2 is phenyl R_1 is amino, C_1—C_5 alkylamino or C_2—C_6 dialkylamino and n is 4.

33. A process as claimed in claim 33 wherein the reaction is carried out in solution in water, dioxane, tetrahydrofuran, dimethylsulphoxide, a lower aliphatic alcohol or a mixture thereof in the presence of from 1 to 5 moles of a basic catalyst per mole of compound of Formula II, the amine of Formula III being present in excess.

34. A process for producing a compound of Formula I substantially as hereinbefore described in any one of Examples 1 to 26.

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35. A method for palliating conditions of depression in warm-blooded animals which method comprises administering to said animal an amount effective as an antidepressant of a compound as claimed in claim 1.

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